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**WO 02/11694 A2**

(54) Title: COMPOSITIONS AND DOSAGE FORMS FOR APPLICATION IN THE ORAL CAVITY IN THE TREATMENT OF MYKOSES

(57) Abstract: A solid dosage form for application in the oral cavity, comprising a poorly bioavailable pharmaceutical active ingredient dispersed in a pharmaceutically acceptable matrix.

Compositions and dosage forms for application in the oral cavity in the treatment of mykoses

5 The present invention relates to solid pharmaceutical dosage forms for application in the oral cavity, comprising a formulation of an antimycotic active ingredient in the form of a solid dispersion of the active ingredient in a pharmaceutically acceptable matrix.

10

The invention also relates to the use of such formulations for manufacture of a medicament for application in the oral cavity in the treatment of mycoses, especially mycosis caused by *Candida albicans*.

15

Furthermore the invention relates to a process for the manufacture of such formulations.

Since administration of drugs in all regions from the neck up  
20 avoids first-pass metabolism, administration in the oral cavity seems to be a very efficacious way to deliver systemic drugs.

This is especially important in the case of pharmaceutically active ingredients which show poor bioavailability due to first  
25 pass metabolism and/or poor water-solubility.

In the treatment of oral mykoses it is particularly advantageous to provide for relatively high local concentrations of the active ingredient in the oral cavity.

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Itraconazol, ( $\pm$ )-cis-4-[4-[4-[4-[[2-(2,4-dichlorophenyl)-2-(1H-1,2,4-triazol-1-yl-methyl)-1,3-dioxolan-4-yl]methoxy]phenyl]-1-piperazinyl]phenyl]-2,4-dihydro-2-(1-methylpropyl)-3H-1,2,4-triazol-3-one, and its pharmaceutically acceptable salts, is known as  
35 an effective active ingredient for oral, parenteral and topic treatment of various types of mykoses. Predominantly, itraconazol is administered orally because of its tendency of extensive tissue distribution.

40 However, since itraconazole is almost insoluble in water (less than 1  $\mu\text{g/ml}$ ), bioavailability is a major problem.

Many attempts have been made to improve the bioavailability of almost insoluble drug compounds. Among them, solid dispersions of  
45 drug and hydrophilic polymers have been suggested to enhance the solubility of the drug.

## 2

WO 97/44014 discloses particles, comprising formulations of itraconazole and water-soluble polymers, said formulations being obtained by melt-extrusion, preferably using hydroxypropyl methylcelluloses as water-soluble polymers. The oral dosage forms disclosed in that document show a remarkably lower food effect.

According to WO 95/31178 mucoadhesive emulsion formulations, comprising itraconazole and cyclodextrins, are useful in the treatment of vaginal infections.

10

The object of the present invention is to provide formulations and dosage forms for application in the oral cavity for the treatment of mykoses, especially mykoses of the oral cavity.

15 Formulations according to the present invention comprise an antimycotic active ingredient in the form of solid dispersions of the active ingredient in a pharmaceutically acceptable matrix, particularly molecular dispersions of the active ingredient in the polymer.

20

Antimycotic active ingredients are preferably compounds with a solubility in water (according to the United States Pharmacopeia XXIII) such that more than 1000 parts of solvent, more preferably more than 10.000 parts of solvent are needed for one part of

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solute.

A preferred active ingredient is the above-identified itraconazole. Other suitable active ingredients are saperconazole, ketoconazole or fluconazole.

30

One preferred embodiment of the invention relates to lozenges.

Another preferred embodiment of the invention relates to solid dosage forms comprising mucoadhesive polymers, preferably tablets for sublingual or buccal application. Tablets for gingival or palatal application are also within the scope of the invention.

35 According to the present invention the active ingredient is homogeneously dispersed in a pharmaceutically acceptable matrix. Preferably, the solid dispersion is in the form of a molecular dispersion of the active ingredient, i.e. a so-called "solid solution". The term "solid solution" is familiar to the skilled person.

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## 3

The pharmaceutically acceptable matrix is based on polymers or low-molecular excipients normally used as fillers for tableting such as for instance sugars or sugar alcohols as matrix building components.

5

Suitable polymers are selected from the group consisting of:

Cellulose derivatives, e.g. alkylcelluloses,  
hydroxyalkylcelluloses, hydroxyalkyl alkylcelluloses.

10

Acrylic polymers of the Eudragit® type like copolymers based on methacrylic acid and methacrylic acid methyl ester

Homo- and copolymers of N-vinylpyrrolidone with Fikentscher K

15 values in the range of from 17 to 100, vinylacetate being a preferred comonomer, e.g. a copolymer obtained from 60 % b.w. of n-vinylpyrrolidone and 40 % b.w. of vinyl acetate

Polyethylene glycols with molecular weights in the range of from  
20 6000 to 100.000 Dalton, polyoxyethylene polyoxypropylene block copolymers

Suitable low-molecular weight matrix components are selected from the group consisting of sugars and sugar alcohols, for example  
25 sorbitol, xylitol, maltitol, erythritol, mannitol, isomalt and the like.

In the case of formulations for lozenges sugar alcohols are preferred matrix components.

30

The amount of matrix building components used in the formulations may range from 5 to 90 % b.w., preferably 10 to 70 % b.w., more preferably 10 to 50 % b.w..

35 Notwithstanding the fact that some of the aforementioned matrix building polymers show mucoadhesive properties, such polymers are only used optionally in formulations for lozenges. However, formulations or finished dosage forms for buccal, sublingual, gingival or palatinal application preferably comprise such  
40 mucoadhesive polymers, optionally in combination with other polymers. Such mucoadhesive polymers are selected from the group consisting of:

Acrylic copolymers of the Eudragit® type

45 Crosslinked polyacrylics (CTFA name: Carbomer)

Sodium carboxymethylcellulose

Tragant gum

Poly(methyl)vinylether-co- maleic acid anhydride  
Alkylcelluloses, e.g. methylcellulose  
Alginates like sodium alginate  
Polyvinylpyrrolidone

5

According to one embodiment of the invention the mucoadhesive polymer is incorporated in the melt formulation.

According to another embodiment of the invention the solid  
10 dispersions of the active ingredient obtained by melt formulation are mixed with one or more mucoadhesive polymers and subsequently processed to finished dosage forms (tablets). For example, 10 to 70 % b.w. of a solid dispersion of the active ingredient in a pharmaceutically acceptable matrix as outlined above can be mixed  
15 with 30 to 90 % b.w. of mucoadhesive polymers.

In addition the matrix formulations or finished dosage forms may contain conventional pharmaceutical ancillary substances, for example extenders such as silicates or diatomaceous earth, mould  
20 releasers such as stearic acid or salts thereof, wetting agents, preservatives, disintegrants, absorbants, colorants, and the like (cf., for example H. Sucker et al. Pharmazeutische Technologie, Thieme Verlag, Stuttgart 1978). The ancillary substances must be thermally stable at the temperature used in the process for  
25 manufacture used here.

Preferred ancillary substances are flavourings and artificial sweeteners for masking the sometimes unpleasant taste of the drug compounds. Suitable artificial sweeteners are for instance sodium  
30 saccharinate, aspartame, neohesperidine or acesulfame, preferably acesulfame or mixtures comprising acesulfame and aspartame. These sweeteners are used in amounts of from 0.05 to 1.0 % b.w., preferably 0.2 to 0.5 to 0.5 b.w.. Another preferred class of sweeteners are sugar alcohols, preferably xylitol, maltitol or  
35 isomalt. In case sugar alcohols are used as matrix components additional sweeteners normally are not needed. Sugar alcohols can be used in amounts of from 2 to 60 % b.w., preferably 5 to 40 % b.w..

40 A preferred method for manufacturing the formulations and finished dosage forms of the present invention is a melt-extrusion process. A preferred apparatus for such process is an extruder equipped with one or more screws, preferably a twin screw extruder. The mixtures comprising all the components of the  
45 pharmaceutical formulations can be processed at temperatures in the range of from 50 to 180°C, preferably 80 to 160°C. Preferably

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the process is carried out in the absence of solvents, e.g. water or organic solvents.

In addition, small amounts of crosslinked polyvinylpyrrolidone 5 (Kollidon® CL) can be used as taste masking agent.

The molten pharmaceutical mixtures are extruded and the still thermoplastic mass is subsequently shaped. Shaping can take place e.g. by hot cutting the extruded strands to give granules or 10 pellets which can be pressed to tablets in a conventional way.

A preferred method for shaping is a calendering process as described for instance in EP-A 240 906 which comprises that the still deformable extrudate is fed between the surfaces of two 15 counter-rotating molding rolls, the surfaces of said rolls having opposed depressions, whereby, separate tablets having the shape of such depressions are formed. The calender and molding rolls useful for the present invention can be cooled or heated per se and the optimum surface temperature of the rolls for the relevant 20 processing step can be adjusted in this way.

The invention also relates to specifically shaped dosage forms for those formulations comprising mucoadhesive polymers.

25 Preferred dosage forms are lenticular or semi-lenticular tablets which can be round or oval and with an angle  $\alpha$  (see Fig.) between the cross-sectional plane of the tablet and the convex tablet body (tangential area) of less than  $90^\circ$ . Fig. 1 and 2 show such an oval lenticular tablet with a tablet length (a), tablet width (b) 30 and thickness (c). Fig. 3 and 4 show a round lenticular tablet with a diameter (d) and a thickness (c).

For instance, oval lozenges can have a length of from 10 to 20 mm, a width of from 6 to 12 mm and a thickness of from 3 to 35 12 mm. Round lozenges can have a diameter of from 5 to 14 mm and a thickness of from 3 to 10 mm.

In the case of semi-lenticular tablets the lower half of the tablet is essentially planar. Fig. 5 shows a round 40 semi-lenticular tablet, Fig. 6 an oval semi-lenticular tablet. Such tablet forms are especially well suited for buccal, gingival, sublingual or palatal application, since they cause little irritation when positioned in the oral cavity. Also, in view of the low tablet weight generally accepted for buccal forms 45 (up to 200 mg per tablet) the ratio of surface to tablet volume is particularly advantageous because of the large surface. Such tablets can have a length of from 3 to 10 mm, a width of from 2

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to 6 mm, a thickness of from 1.5 to 5 mm (oval forms) or a diameter of from 3 to 10 mm and a thickness of from 1.5 to 5 mm (round forms). Round semi-lenticular tablets are preferred.

5 Such dosage forms can be manufactured using a calendering process as described above. In the case of semi-lenticular tablets only one of the calender rolls is having depressions, whereas the other roll is planar.

10 Another method for manufacturing semi-lenticular tablets is by shaping the melt with the aid of a rotating perforated roll into drops which are subsequently solidified by cooling.

The dosage forms obtained according to the present invention are  
15 particularly useful in the treatment of oral mykoses.

Surprisingly, the solid solutions according to the present invention deliver the active ingredient without substantial recrystallization in an aqueous environment like the oral cavity,  
20 thus achieving sufficient plasma levels.

Therefore, the dosage forms according to the invention are useful in the treatment of diseases of the oral cavity by delivering high local concentrations as well as in systemic treatment.

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#### Examples

#### General Method

30 Tablets were produced starting from molten mixtures of the components and extruding said mixtures using a twin screw extruder (Leistritz Micro 18). The still thermoplastic extrudate was calendered as described in EP-A 240 906 to give oval lozenges of 17,4 mm length, 8.5 mm width and 4.7 mm thickness with a mean  
35 tablet weight of 450 mg.

The dissolution rates were determined according to the USP-paddle model at 50 rpm. 37°C, no change pH 1.0 (0.5 % SDS).

40 The formation of solid solutions was determined by DSC (Differential Scanning Calorimetry) measurements using a Mettler TA 4000 System.

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## Example 1

Itraconazol	20 % b.w.
Hydroxypropylcellulose	80 % b.w.
5 Melt temperature:	133°C
Dissolution: 95 % after 8 h	

## Example 2

10 Itraconazol	20 % b.w.
Hydroxypropylcellulose	70 % b.w.
Hydroxypropylmethylcellulose	10 % b.w.
Melt temperature:	135°C
Dissolution: 77 % after 8 h	

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## Example 3

Itraconazol	20 % b.w.
N-vinylpyrrolidone vinylacetate	
20 Copolymer (VP/Vac 60/40)	60 % b.w.
Hydroxypropylcellulose	10 % b.w.
Melt temperature:	152°C
Dissolution: 93 % after 8 h	

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## Claims

1. A solid dosage form for application in the oral cavity,  
5 comprising a poorly bioavailable pharmaceutical active ingredient dispersed in a pharmaceutically acceptable matrix.
2. A dosage form according to claim 1, wherein the active ingredient is molecularly dispersed in the matrix.
- 10 3. A dosage form according to claims 1 or 2, wherein the solubility of the pharmaceutically active ingredient in water is such that more than 10.000 parts of water are needed for one part of active ingredient.
- 15 4. A dosage form according to any of claims 1 to 3, comprising itraconazole as active ingredient.
5. A dosage form according to any of the claims 1 to 4 in the  
20 form of a lozenge.
6. A dosage form according to claim 5 comprising one or more sugar alcohols as matrix components.
- 25 7. A dosage form according to any of the claims 1 to 4, comprising mucoadhesive polymers.
8. A dosage form according to claim 7, wherein the mucoadhesive polymer is a crosslinked polyacrylic acid.
- 30 9. A dosage form according to claim 7, wherein the mucoadhesive polymer is a poly(meth)acrylate.
10. A dosage form according to any of the claims 7 to 9 in  
35 the form of a tablet for buccal, sublingual, gingival or palatal application.
11. A dosage form according to claim 10, consisting of lenticular or semi-lenticular shaped tablets.
- 40 12. A dosage form according to any of claims 1 to 11, obtained by a melt-extrusion process.

13. The use of dosage forms according to any of claims 1 to 12 for the manufacture of a medicament for the treatment of mykoses.

5 14. The use according to claim 13 for the manufacture of a medicament for the treatment of oral mykoses.

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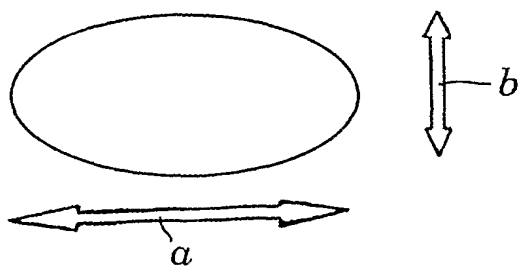
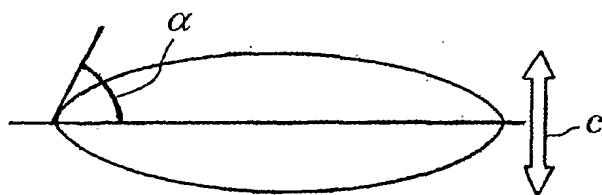
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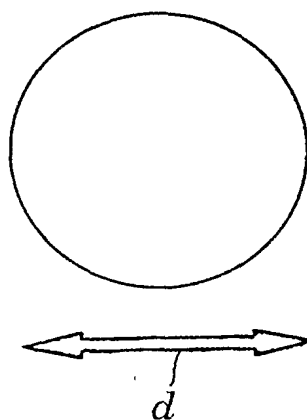
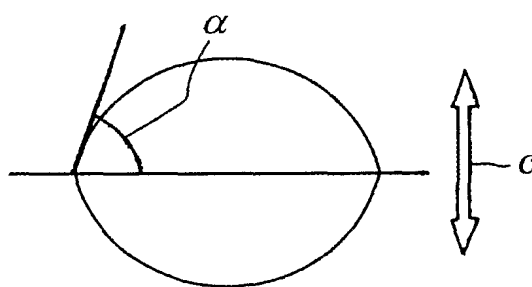
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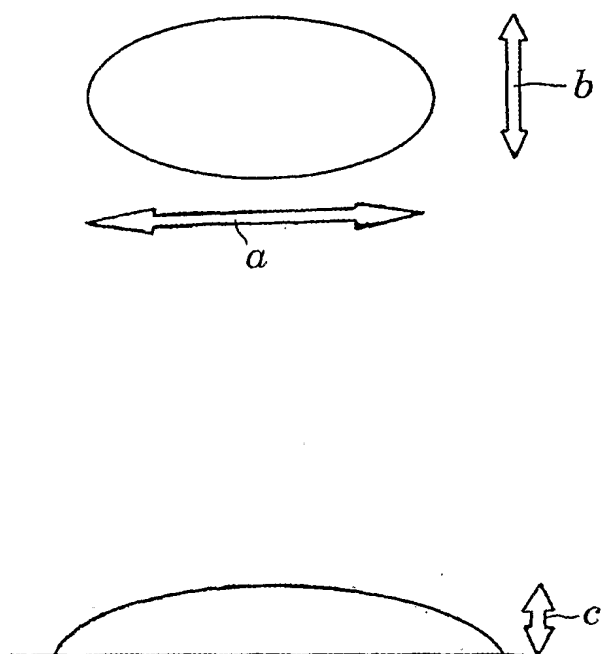
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*Fig. 1**Fig. 2*

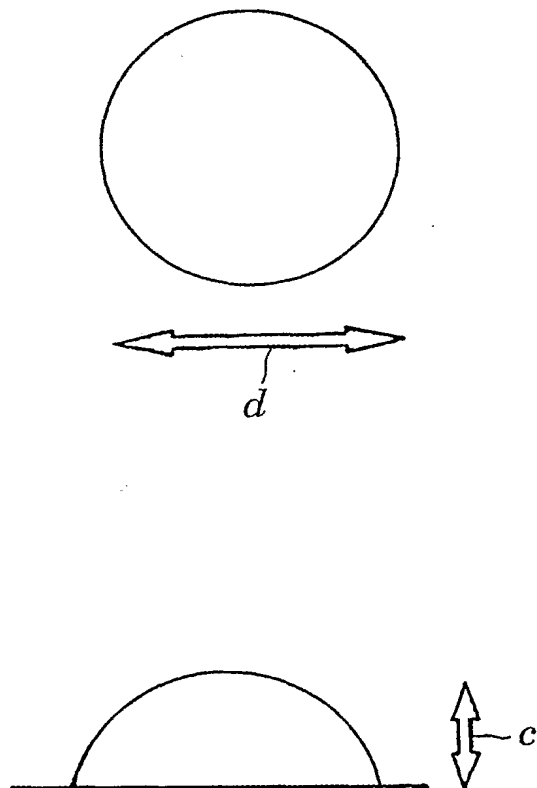
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*Fig. 3**Fig. 4*

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*Fig. 5*

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*Fig. 6*

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(57) Abstract: A solid dosage form for application in the oral cavity, comprising a poorly bioavailable pharmaceutical active ingredient dispersed in a pharmaceutically acceptable matrix.

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**A. CLASSIFICATION OF SUBJECT MATTER**  
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According to International Patent Classification (IPC) or to both national classification and IPC

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)

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Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, BIOSIS, CHEM ABS Data, MEDLINE, EMBASE

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

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☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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